Twin Registry. The criticisms of the Twin Registry noted here should also be compared with a subsequent letter by Burch (Lancet 1: 1283, 1972) and Letters to the Editor from Cherry and Forbes (Lancet 14 October, 1972) and Friberg (Lancet 4 November 1972). These are reproduced below.

SMOKING AND HEALTH

SIR,—Are we to judge from their silence that Dr. [illegible]'s critics have conceded his case (Jan. 29, p. 243, and [illegible] 11, p. 586)? Is cigarette-smoking non-lethal?

[illegible]he undoubted positive associations between cigarette [illegible]ing and death-rates from various diseases are not [illegible]al in origin, an alternative explanation is needed. [illegible]rding to Fisher,[1] such associations might arise from [illegible]nstitutional factors. That is to say, one or more of the [illegible]s that predispose to certain forms of smoking might be [illegible]ame as, or linked with, genes that predispose to fatal [illegible]ders such as lung cancer. In principle, we can dis-[illegible]inate between causal and constitutional hypotheses by [illegible]ining deaths in series of twins discordant for smoking [illegible]. The straightforward causal hypothesis predicts [illegible] deaths will occur earlier, on the average, in the smoking [illegible]bers of both monozygotic and dizygotic twin pairs. [illegible] constitutional hypothesis predicts that "early deaths" [illegible]ccur with equal frequency, on the average, among the [illegible]ing and the non-smoking members of monozygotic [illegible] pairs: where dizygotic twins are concerned, smokers [illegible]ld suffer an excess frequency of "early deaths" over [illegible] smokers.

[illegible]his simple test of the two hypotheses is, of course, [illegible]ered by the rarity of monozygotic twins discordant [illegible]moking habits: only some 20–25% have been found [illegible]e strikingly discordant.[1,2]

[illegible]espite this obstacle, Friberg et al.[3] have obtained some [illegible]ging results. They studied deaths among 246 male [illegible]126 female monozygotic twin pairs, and in 706 male [illegible]781 female dizygotic twin pairs appreciably discordant [illegible]on-smoker" versus "smoker"; "less exposed" [illegible]us "more exposed"), and born in Sweden between [illegible]0 and 1925. Among the dizygotic male twins, deaths [illegible]re recorded over a standard period as follows: 13 of [illegible]"non-exposed and less-exposed" as compared with [illegible]f the "smoker and more exposed". Among dizygotic [illegible]ale pairs, deaths were recorded in 18 of the "non-[illegible]osed and less-exposed" and 20 of the "smoker and [illegible]re exposed". Results for discordant monozygotic twins [illegible]re very interesting: 14 deaths were recorded among [illegible]e "non-exposed and less-exposed" men, but only 9 [illegible]ong the "smokers and more exposed"; among the [illegible]men, 4 of the "non-exposed and less-exposed" and 6 of [illegible]e "smoker and more exposed" died. Overall, the "more [illegible]osed" (sexes combined) enjoyed a slight but not signifi-[illegible]t advantage (18/15) over the "non-exposed and less-[illegible]posed". On a formal statistical test, the difference in mor-[illegible]ity ratios ("non-exposed and less-exposed"/"smoker [illegible]more exposed") between the sets of monozygotic and [illegible]gotic male twins corroborates the constitutional hypo-[illegible]is and rejects (at the 1–2% level) the causal hypothesis [illegible]with Yates' correction = 5·78; 0·01 < P < 0·02). How-[illegible]r, this result needs to be treated with caution because [illegible]e degree of discordance for smoking habits between the [illegible]monozygotic and dizygotic series, although similar, was [illegible]ably not identical. This reservation apart, the indepen-[illegible]t findings of Friberg et al.[3] support Dr. Seltzer.

[illegible]Perhaps the issue could be put beyond reasonable doubt [illegible]supplementing the study of Friberg and his colleagues [illegible]a world-wide survey under the ægis, say, of the World Health Organisation? And why should not the cigarette manufacturers foot the bill?

[illegible] General Infirmary,

P. R. J. BURCH.

SMOKING AND HEALTH

SIR,—Professor Burch [1,2] calls for a worldwide twin study to distinguish between causal and constitutional factors in the association between cigarette smoking and disorders such as coronary heart-disease and lung cancer. This proposal is based on the results obtained by Friberg et al.[3] for monozygotic and dizygotic twins which suggest to Friberg and Burch that differences in mortality between populations of smokers and non-smokers are a consequence of differences in genetic and other inherited factors.

This interpretation of Friberg's results is open to several criticisms. First, the published data provide no direct information about differences in mortality within individual *pairs* of twins. That is, the data only provide information about deaths in two populations, each member of which happens to have a twin in the other population; it is not stated in how many instances both, one, or no twins in a pair have died. Hence, data permitting comparisons within twin pairs, where one twin serves as a control for the other (which represents the unique value of this type of experiment), are not available to the reader. For example, for monozygotic twins, where Friberg observes approximately equal numbers of deaths for non-smokers and smokers—viz., 4 vs 5, and 4 vs 6 deaths, respectively; for males and females, it is possible that, on average, the smokers died at an early age.

Secondly, it must be noted that some of the reported data only represent approximations, since two groups of smokers have overlap; a "less exposed" group, which is considered with non-smokers, includes smokers of up to 20 cigarettes per day, whereas a "more exposed" group, which is considered with smokers, includes smokers of down to 10 cigarettes per day. Such an approach does not provide a clear distinction between categories of amounts smoked. Also, the intra-pair differences to smoking exposure might be less for the monozygotic than for the dizygotic pairs, because of constitutional factors which might cause smoking discordancy.

For these and other reasons, it is appropriate to re-examine the methods of presentation and analysis. A discussion along these lines has been presented previously.[4]

The evidence linking cigarette smoking causally to various diseases has, for some time, been sufficiently strong to concentrate efforts on reducing or eliminating the hazards of cigarette smoking.[5–8] This conclusion does not deny the fact that there remain numerous questions concerning the action of cigarette smoking, which remain to be solved. One of these is the role of genetic factors which may contribute to a person taking up various forms of smoking or contracting individual diseases. A worldwide twin study, as suggested by Professor Burch, would take a number of years to complete; and since, at present, there is little evidence that such a study would alter the main conclusions concerning the effects of cigarette smoking on health, a lower priority should be given to such a study than to research on reducing the accepted hazards.

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W. H. CHERRY
W. F. FORBES.

SMOKING AND HEALTH

SIR,—In the comments of Dr. Cherry and Professor Forbes (Oct. 14, p. 824) on the proposal of Professor Burch [1,2] to embark on worldwide twin studies, our report from the Swedish registry on mortality in smoking discordant monozygotic and dizygotic twins [3] is criticised to some extent.

Dr. Cherry and Professor Forbes point out that the data provide no information on what has happened within the individual *pairs* of twins, since it was not stated in how many instances both, one, or no twins in a pair had died. We agree that such analysis is of importance where a substantial number of concordant deaths occur. Concerning the crucial group (male twin pairs born 1901–25), where differences between dizygotic and monozygotic twins were found, however, only one pair in the dizygotic group (non-smoker/smoker in age-group 1901–10) and one pair in the monozygotic group ("less exposed"/"more exposed" in age-group 1901–10) showed concordant death. Thus the findings reported actually refer to differences within individual *pairs* of twins. For our future reports, when a larger number of concordant deaths can be expected, no doubt one should also take the year of death into consideration. At the time of our report [4] such an analysis would not have been meaningful.

We appreciate the comments, but when Dr. Cherry and Professor Forbes mean that what they point out may invalidate our interpretation of the data presented, we must disagree. Also, we are surprised about their comments, because already, in a personal letter, Professor Forbes received a complete set of data showing the number of twins in the mentioned age-groups, divided into dizygotic and monozygotic pairs, from which it was easily seen in how many instances both, one, or no twins in a pair had died.

Dr. Cherry and Professor Forbes are sceptical of Professor Burch's proposal of worldwide twin studies. One reason given is that, at present, there is little evidence that such studies would alter the main conclusions concerning the effects of cigarette smoking on health. For certain pulmonary diseases (e.g., lung cancer) the causal relationship with cigarette smoking is quite clear. On the other hand, twin studies might well be of substantial value even for these effects—for example, to find out whether certain persons are more susceptible than others to an effect of cigarette smoking. For other effects, including high mortality in general and particularly, for example, in coronary heart-disease, we feel that the case against cigarette smoking per se is not all that strong and in our opinion international collaboration using twins as target populations would be extremely useful. The problem in twin studies, even using a population the size of Sweden's, is to get enough numbers in different, well-defined smoking discordant groups. We are happy to learn that Dr. Cherry and Professor Forbes do not live up to their own objections to creating new registries. As can be seen in a recent paper of theirs,[9] they state, "A twin study is being planned, partly to investigate further the observations, on smoking discordant twins, reported by Friberg et al."

Finally, we wish to point out that international collaboration on twin studies should not be carried out with the sole aim of studying effects of tobacco on health. Certainly, as was pointed out at an international symposium on twin registries in the study of chronic disease,[6] in advocating the establishment of new large-scale twin registries, it should be recognised that such registries constitute valuable national resources for investigations into the causes and prevention of disease. While large-scale twin studies until now have primarily focused on the health consequences of smoking, the twin method has a much broader applicability to a large number of medical and social problems concerned with the interrelationships between environmental agents and their impact upon the genetic constitution. The importance of these interrelationships was precisely the reason for a recent expansion of the Swedish twin registry in collaboration with the National Environment Protection Board to include an additional 15,000 pairs born from 1926 to 1942.

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LARS FRIBERG.